

REMARKS

In the Office Action mailed November 17, 2003, the Examiner alleges that the reply filed on "March 10, 2003" was not fully responsive. Applicants respectfully point out, for clarity only, that the reply (to the Office Action mailed February 25, 2003) was actually filed on "July 25, 2003." In particular, the Examiner contends that the reply directed the entry of new claim 21, while new claims 22-32 were attached. In response to the Examiner's latest communication, Applicants have cured the defect by directing the entry of new claims 21-32.

Claims 1-3, and 14-32 are pending. Claims 4-5 have been canceled. Applicants reserve the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications. Claims 1 and 14-20 have been amended and Claims 21-32 has been added to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Support for the amended and new claims may be found in the specification. Specifically, examples of support for claims 1 and 15-18 can be found on page 16, 5-7 lines, page 25, lines 12-14, page 26, lines 15-20, and page 32, lines 15-20 of the instant specification. Examples of support for claims 14 and 19-20 can be found on page 22, lines 17-23, page 25, lines 24-25, page 26, lines 12-20, and page 48, lines 12-22 of the instant specification. Examples of support for claim 21 can be found on page 16, 5-7 lines, page 25, lines 12-14, page 26, lines 15-20, and page 32, lines 15-20, page 45, line 24 to page 46, line 7 and page 48, lines 12-22 of the instant specification. Examples of support for claims 22 and 27-30 can be found on page 16, 5-7 lines, page 20, lines 14-16, page 25, lines 12-14, page 26, lines 15-20, and page 32, lines 15-20 of the instant specification. Examples of support for claims 23-24 can be found on page 15, lines 9-13 and page 20, lines 14-16 of the instant specification. Examples of support for claims 25-26 and 31 can be found on page 20, lines 14-16, page 22, lines 17-23, page 25, lines 24-25, page 26, lines 12-20, and page 48, lines 12-22 of the instant specification. Examples of support for claim 32 can be found on page 16, 5-7 lines, page 20, lines 14-16, page 25, lines 12-14, page 26, lines 15-20, page 32, lines 15-20, and page 45, line 24 to page 46, line 7 and page 48, lines 12-22 of the instant specification. Thus, the new and amended claims are fully supported by the instant specification and no new matter has been introduced.

The Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 1-5, 14, and 15 are rejected under 35 U.S.C. § 112, first paragraph for lack of written description. The Examiner asserts that the specification allegedly fails to provide a sufficient description of ETB antagonists for use in the methods of the invention. This rejection is in error and should be withdrawn.

The Examiner alleges that Applicants fail to disclose a representative number of species in the allegedly broad genus of selective ETB antagonists. The currently pending claims embrace the use of peptides, small molecules, ETB antibodies, and ETB antisense molecules as selective ETB antagonists. Applicants believe that the specification adequately describes these classes of compounds that have selective ETB antagonist activity that can be used in accordance with the methods of the invention.

The present invention as claimed relates to methods for treating cancer comprising administering a compound that is a selective or specific antagonist of ETB. In accordance with the invention as claimed and described in the specification, selective or specific antagonists of ETB encompass peptide inhibitors, small molecule inhibitors, antibodies, and antisense molecules. As described in the specification, ETB activity is responsible for the downregulation of E-cadherin, β -catenin, and p120^{CTN} proteins and the increased activity of caspase 8, early events associated with the development of cancer. These activities are mediated through ETB signaling and not through ETA signaling (*e.g.*, page 22, lines 17-31, page 48, lines 12-22 and page 49, lines 13-14). Therefore a therapeutic agent that is to be used in accordance with the invention is one that specifically inhibits ETB signaling, not ETA signaling. Thus, a selective or specific ETB antagonist as described by the instant specification is one that inhibits ETB specific activity, *e.g.*, i) prevents downregulation of E-cadherin, ii) prevents downregulation of β -catenin, iii) prevents downregulation of p120^{CTN}, iv) prevents increased activity of caspase 8. It is ETB activity which is responsible for these events, not ETA activity. A compound is considered specific for the inhibition of ETB, and not specific for ETA, if it inhibits any one of the ETB specific activities described.

The specification provides specific examples of the compounds that demonstrate activity as selective or specific ETB antagonists such as BQ788, IRL-1038, and RES-701-1 (*e.g.*, page 16, lines 8-13 of the instant specification). These compounds act as selective or specific ETB antagonists in that they prevent downregulation of E-cadherin, prevent downregulation of β -catenin, and/or prevent downregulation of p120^{CTN} (*e.g.*, page 24, lines

26-28 and page 48, lines 15-19 of the instant specification). The specification also provides examples of the types of activities that an ETB selective or specific antagonist would be expected to demonstrate and provides numerous assays which could be utilized to identify whether a compound is a selective ETB antagonist (*e.g.*, Sections 5.6.1 and 5.6.2 of the instant specification).

Furthermore, at the time the instant specification was filed, numerous examples of selective or specific ETB antagonists were known in the art. The use of such known selective ETB antagonists is encompassed by the methods of the invention (*e.g.*, page 16, lines 5-6 and page 20, lines 14-18 of the instant specification). Appendix A attached hereto is a non-exhaustive list of ETB selective or specific antagonists that were known on or before the filing date of the instant application. For example, a number of selective non-peptide small molecule inhibitors of ETB were known at the time of filing of the instant specification. Pharmacodynamic and pharmacokinetic profiles of two small molecule inhibitors of ETB, Ro 46-8443 and A-192621, were disclosed by Douglas (1997, *TiPS* 18:408-412 on page 410, column 3, lines 1-14 and Table 4, submitted herewith as Reference C07). In addition to Ro 46-8443 and A-192621, the class of known small molecule (non-peptide) specific inhibitors of ETB includes PD 147452 and PD 151583 (Battistini and Dussault, 1998, *Pulmonary Pharmacology & Therapeutics* 11:97-112 on page 101, column 2, lines 3-10 and Table 1, submitted herewith as Reference C03).

Prior to the filing date of the instant specification, the structural features that allow non-peptide small molecules to specifically inhibit ETB over ETA were characterized. Studies were conducted to modulate selective ETA antagonists to produce antagonists that were increasingly specific for ETB (Chan et al., 1998, *Bioorganic & Medicinal Chemistry* 2301-2316, submitted herewith as Reference C04; Mederski et al., 1999, *Bioorganic & Medicinal Chemistry Letters* 9:619-22, submitted herewith as Reference C08). Examples of such selective ETB antagonists include Compounds 4c, 4f, 4h-4l, 6b, 6c, 6e, 6f, and Compounds 7aa-7ff (see page 2304, column 1, lines 29-33; page 2304, column 2, lines 14-21; and page 2306, column 22, lines 27-33 of Reference C04 and page 622, line 8-11 of Reference C08, respectively). Not only was one skilled in the art able to identify a specific ETB antagonist, he was also able to modify existing compounds to create a specific ETB antagonist. Thus, one of skill in the art would not only know the structure of the small molecule compounds which could be used in the methods of the invention but also the

relationship between that structure and the compound's ability to function as a selective or specific ETB antagonist.

The sequence of ETB was known and publicly available at the time of filing the instant specification (*e.g.* Genbank Accession Nos. AF114165, NM_000115, NM_003991, and U87460). Using this information in conjunction with the teachings of the instant specification regarding making and using ETB antisense (Section 5.3 on pages 26-32 of the instant specification) and ETB antibodies (Section 5.4 on pages 32-34 of the instant specification), one of skill in the art could easily produce species of those compound classes. In fact, prior to the filing date of the instant specification, antisense had been used to decrease ETB expression (D'Orléans-Juste et al., 1997, *Molecular and Cellular Biochemistry* 172:199-211 and Adner et al., 1994, *European Journal of Pharmacology* 261:281-4, submitted herewith as References C06 and C01, respectively). ETB antibodies had been also been produced using standard molecular biological techniques (Barber et al., 1996, *American Journal of Physiology* 270:H65-71 and Ninomiya et al., 1998, *J. Pharmacol. Exp. Therap.* 286:469-80, submitted herewith as References C02 and C09, respectively).

Thus, the disclosure of the instant specification combined with what was known to one of skill in the art would have motivated evaluation of such compounds for anti-cancer activity as taught by the Applicants' disclosure. The specification need not disclose what one skilled in the art already possesses. Hirschfeld v. Banner, Commissioner of Patents and Trademarks, 200 U.S.P.Q. 276, 281 (D.D.C. 1978), aff'd, 615 F.2d 1368 (D.C. Cir. 1980), cert. denied, 450 U.S. 994 (1981). A patent application need not include in the specification that which is already known to and available to the public. Paperless Accounting Inc. v. Bay Area Rapid Transit System, 804 F.2d 659, 231 U.S.P.Q. 649 (Fed. Cir. 1986), cert. denied, 480 U.S. 933 (1987).

The instant specification teaches methods of using specific ETB antagonists to treat cancer. Members of the genus of compounds described for use in the methods of the invention were available at the time of filing and could be readily recognized based on the disclosure by one of skill in the art. The fact that Applicants did not recite these compounds verbatim in the specification should not preclude the specification from meeting the written description requirement. In re Alton, 76 F.3d 1168, 1172, 37 U.S.P.Q.2d 1578, 1581 (Fed. Cir. 1996) (emphasis added, citations omitted):

The adequate written description requirement, which is distinct from the enablement or best mode requirements, serves “to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; *how the specification accomplishes this is not material.*” In order to meet the adequate written description requirement, the applicant *does not have to utilize any particular form of disclosure* to describe the subject matter claimed, but “the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.”

The Examiner seems to be construing the fact that “very few selective ETB antagonists have been discovered” (page 10, line 23 of the instant specification) as an admission by Applicants that it is difficult to produce compounds with the desired activity of selectively antagonizing ETB. However, Applicants believe the statement should be construed as a fact, without importing a reason as to why that fact is so. For example, rather than an inability to produce such compounds, there may have been a lack of interest in ETB selective antagonists thus far. In fact, Davenport and Battistini (2002, *Clinical Science* 103:1S-3S, submitted herewith as Reference C05) agree that, as compared to selective ETA antagonists and non-selective ETA/ETB antagonists, “a limited number of peptide and non-peptide ETB receptor antagonists have been developed, reflecting the lack of clinical need for this type of compound” (page 2S, column 2, second full paragraph). Applicants believe that the instant specification provides a heretofore unappreciated reason for clinical interest in such compounds.

In view of the foregoing, Applicants request that the Examiner withdraws the rejection under 35 U.S.C. § 112, first paragraph.

The Rejections Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 1-4 and 14-18 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,063,911 by Vournakis et al. (“Vournakis”). Claims 1-4 and 14-18 are also rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,382,569 by Cody et al. (“Cody”). The Examiner alleges that Vournakis and Cody teach non-peptide, selective inhibitors of ETB for use in the claimed methods. Applicants respectfully disagree.

The Examiner argues that, although Ro61 disclosed in Vournakis and the compounds disclosed in Cody are *non-specific* non-peptide inhibitors of *both* endothelin

receptors, they are nonetheless still encompassed by the currently pending claims. The Examiner points out that the instant specification does not define ETB selective antagonist and, as such, the compounds of Vournakis and Cody cannot be excluded from this class of compounds.

Applicants point out that the present invention relates to the treatment and prevention of cancers using compositions specifically inhibit ETB activity (*e.g.*, downregulation of E-cadherein and β -catenin proteins), events that are associated with cancer development (*e.g.*, page 15, lines 9-21 of the instant specification). Applicants have demonstrated in the working examples that ETB activity, rather than ETA activity, is responsible for the downregulation of E-cadherein and β -catenin (*e.g.*, page 22, lines 17-31, page 48, lines 12-22 and page 49, lines 13-14). In accordance with the present invention, any therapeutic agent that is *specific* for inhibiting ETB activity should act to inhibit the early events of cancer. Thus, a therapeutic agent that inhibits both ETB and ETA with equal effectiveness (*e.g.*, non-specific) would not be a *selective* or *specific* inhibitor of ETB.

Contrary to the Examiner's assertion, the specification has defined what is meant by "specific" or "selective antagonists of ETB," and has used these terms consistently with the ordinary and customary use of these terms in the art. Furthermore, the art at the time of filing, continuing through to present day, is replete with examples of how the term "ETB selective antagonist" is meant by those of skill in the art. For example, Davenport & Battistini (Reference C05) state that "antagonists are currently classified as ETA-selective, ETB-selective, or mixed antagonists that display similar affinities for both receptor subtypes." (see page 1S, column 2, last paragraph of Reference C05). Inhibitors of endothelin receptors can be 1-2 orders of magnitude more selective for one receptor type than the other and still be considered ETA or ETB selective or specific antagonists (page 2S, column 2, second to last paragraph of Reference C05). Battistini & Dussalt (Reference C03) classify various peptide and non-peptide antagonists of the endothelin receptors as either ETA selective or specific inhibitors, ETB selective or specific inhibitors, or ETA/ETB mixed inhibitors based on the K_i or IC_{50} for each compound at each receptor type (see Table 3 of Reference C03). Additionally, the specification adheres to the art-accepted meaning of "ETB selective antagonist" by referring to BQ788 as a selective or specific ETB antagonist (*e.g.*, page 48, lines 15-17 of the instant specification). The Examiner's interpretation of the term "ETB selective antagonist" as any compound that binds the ETB receptor and is therefore selective cannot be reconciled with the art-accepted term that one

of skill in the art would recognize. Thus, “ETB selective antagonist” does have a particular meaning both in the specification and in the art and can therefore be construed as a claim limitation - - a limitation that neither Vournakis or Cody discloses.

Furthermore, the Examiner alleges that the claims encompass therapeutic agents that are ETB selective antagonists as well as ETA/ETB non-selective antagonists. However, taken to the extreme, that Examiner’s interpretation of the term “ETB selective antagonist” is broad enough to encompass ETA selective antagonists as well. For example, the art and the specification characterize BQ123 as a selective ETA antagonist (*e.g.*, page 48, lines 15-17 of the instant specification). BQ123 has a K_i of 22nM and 18,000nM for ETA and ETB, respectively (Table 3 on page 104 of Battistini and Dussault, Reference C03). However, Applicants point out that, although the peptide inhibitor has at least a 818-fold selectivity for ETA over ETB, it does bind and inhibit ETB when present at high enough concentrations. According to the Examiner’s interpretation, BQ123 could be used in the methods of the invention as a “ETB selective antagonist.” Upon reading the specification, one of skill in the art would immediately realize that this is not the case. In fact, the working examples demonstrate unequivocally that BQ123 or similar compounds do not produce the required inhibition of early events in cancer progression that are encompassed by the methods of the invention (*e.g.*, page 48, lines 12-22 of the instant specification). Thus, the Examiner’s interpretation of the term “ETB selective antagonist” is inconsistent with the use of the term in the specification and its common and ordinary meaning. Vournakis and Cody characterize the compounds described therein as a non-specific, non-peptide inhibitor of both endothelin receptors (*e.g.*, column 3, lines 44-46 of Vournakis) and antagonists of endothelin¹ (*e.g.*, column 38, lines 3-4 of Cody), respectively.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 1 U.S.P.Q.2d 1081 (Fed. Cir. 1985). “Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. . . .” Structural Rubber Prod. Co. v. Park Rubber Co., U.S.P.Q. 1264 (Fed. Cir. 1984). If it is necessary to reach beyond the boundaries of a single reference to provide a missing disclosure of the claimed invention, it is not a § 102

¹ Since endothelin binds both ETA and ETB, an endothelin antagonist would inhibit activities from *both* ETA and ETB. Thus, an endothelin antagonist is not selective or specific for ETB.

anticipation. Scripps Clinic & Research FDN. v. Genentech Inc., 927 F.2d 1565, 18 U.S.P.Q.2d 1869 (Fed. Cir. 1991). Furthermore, anticipation is not shown even if the differences between the claims and the prior art reference are argued to be "insubstantial" and the missing elements could be supplied by the knowledge of one skilled in the art. Structural Rubber Prod. Co. v. Park Rubber Co., 221 U.S.P.Q. 1264 (Fed. Cir. 1984).

Disclosure of a non-selective ETA/ETB antagonist (*e.g.*, a compound which antagonizes both ETA and ETB) for use in the methods of the present invention would not meet the aforementioned criteria. Such a non-selective antagonist would inhibit ETA function at the concentration which would inhibit ETB function, thus both receptors would be inhibited. In such a situation, the early events associated with cancer development would not be *selectively* inhibited (as the specification discloses) because events unrelated to cancer development, but resulting from ETA-related signaling, would also be inhibited. Thus, neither Vournakis nor Cody meet each and every claim limitation and therefore do not anticipate the claimed invention.

In view of the foregoing, Applicants request that the Examiner withdraws the rejections under 35 U.S.C. §102.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

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Respectfully submitted,

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APPENDIX A

ETB selective antagonist	Class of Inhibitor	Reference
Ro 46-8443	non-peptide small molecule	Breu et al., 1996, <i>FEBS Lett.</i> 383:37-41 and Douglas, 1997, <i>TiPS</i> 18:408-412
A-192621	non-peptide small molecule	Douglas, 1997, <i>TiPS</i> 18:408-412 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
PD 147452	non-peptide small molecule	Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
PD 151583	non-peptide small molecule	Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
Compound 4c	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 4f	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 4h	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 4i	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 4j	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 4k	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 4l	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 6b	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 6c	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 6e	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 6f	non-peptide small molecule	Chan et al., 1998, <i>Bioorganic & Medicinal Chemistry</i> 2301-2316
Compound 7aa	non-peptide small molecule	Mederski et al., 1999, <i>Bioorganic & Medicinal Chemistry Letters</i> 9:619-22

ETB selective antagonist	Class of Inhibitor	Reference
Compound 7bb	non-peptide small molecule	Mederski et al., 1999, <i>Bioorganic & Medicinal Chemistry Letters</i> 9:619-22
Compound 7cc	non-peptide small molecule	Mederski et al., 1999, <i>Bioorganic & Medicinal Chemistry Letters</i> 9:619-22
Compound 7dd	non-peptide small molecule	Mederski et al., 1999, <i>Bioorganic & Medicinal Chemistry Letters</i> 9:619-22
Compound 7ee	non-peptide small molecule	Mederski et al., 1999, <i>Bioorganic & Medicinal Chemistry Letters</i> 9:619-22
Compound 7ff	non-peptide small molecule	Mederski et al., 1999, <i>Bioorganic & Medicinal Chemistry Letters</i> 9:619-22
hET _B -AS	antisense	Adner et al., 1994, <i>European Journal of Pharmacology</i> 261:281-4 and D'Orléans-Juste et al., 1997, <i>Molecular and Cellular Biochemistry</i> 172:199-211
anti-ETB (conserved middle region)	antibody	Barber et al., 1996, <i>American Journal of Physiology</i> 270:H65-71
anti-ETB (carboxy terminal)	antibody	Ninomiya et al., 1998, <i>J. Pharmacol. Exp. Therap.</i> 286:469-80
BQ788	peptide	Ishikawa et al., 1994, <i>Med. Sci.</i> 91:4892-6 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
IRL-1038	peptide	Karaki et al., 1993, <i>Eur. J. Pharmacol.</i> 231:371-4 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
RES-701-1	peptide	Yamasaki et al., 1994, <i>J. Antibiot. Tokyo</i> 47:276-80 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
RES-701-3	peptide	Yamasaki et al., 1994, <i>J. Antibiot. Tokyo</i> 47:276-80 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
BQ-017	peptide	Fukami et al., 1996, <i>J. Med. Chem.</i> 39:2313-30 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
IRL 2500	peptide	Balwierzczak et al., 1995, <i>J. Cardiovasc. Pharmacol.</i> 26:S393-6 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112

ETB selective antagonist	Class of Inhibitor	Reference
IRL 2659	peptide	Balwierczak et al., 1995, <i>J. Cardiovasc. Pharmacol.</i> 26:S393-6 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112
IRL 2796	peptide	Balwierczak et al., 1995, <i>J. Cardiovasc. Pharmacol.</i> 26:S393-6 and Battistini and Dussault, 1998, <i>Pulmonary Pharmacology & Therapeutics</i> 11:97-112